

JAUNDICE FOLLOWING ACETARSOL PESSARIES*

BY

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Whereas most cases of jaundice occurring during therapy with arsenicals are due to a viral hepatitis, some appear to result from a toxic or allergic action of arsenic producing an intra-hepatic obstructive jaundice.

Case History

Miss X, a machinist, aged 19 years, consulted her doctor on 8. 11. 50 because she had a whitish vaginal discharge. Acetarsol pessaries were prescribed, and she was told to insert one pessary into the vagina daily. On 11. 11. 50 she complained of shivering, fever, oedema of the eyelids, lips, and face, and chemosis. There was a morbilliform eruption on the trunk, forearms, and arms. On 14. 11. 50 she complained of anorexia, nausea, vomiting, jaundice, and pruritis. The pruritis and jaundice increased in severity with loss of weight until she was admitted to hospital on 29. 11. 50. The pyrexia, anorexia, nausea, and vomiting were present for a few days. Her urine became dark and her stools pale. The pessaries were discontinued on the appearance of jaundice. There was no abdominal pain or discomfort, and no hepatic or splenic enlargement or tenderness before admission.

Past History.—There was no history of venereal disease, nor of any previous attacks of allergy, jaundice, gall-stones, or gall bladder disease. Neither arsphenamine nor acetarsol had previously been administered, nor had she received any blood, serum, or other intravenous therapy. She had been given penicillin after a forceps delivery on 23. 8. 50.

Examination.—A thin, deeply jaundiced patient, the jaundice being of a greenish-yellow colour. She was not drowsy, nor obviously ill. The lungs, heart, and central nervous system were normal, the blood pressure was 130/70. Many scratch marks appeared on the skin over the interscapular region, trunk, forearms, legs, hands, and feet. There was no exfoliation or hyperkeratosis.

Investigations

29. 11. 50—3. 12. 50. Daily urine tests showed bilirubin present in large amounts. Urobilinogen not detected.
30. 11. 50 Total R.B.C.—4,020,200/c.mm.
90 per cent. Hb (Sahli) 12.6 g./100 ml.
Total W.B.C.—4,800/cu. mm.
Neutrophil polymorphs — 44 per cent.
Lymphocytes — 40 per cent.
Eosinophils — 9 per cent.
Monocytes — 6 per cent.
Basophils — 1 per cent.
Appearance of film—normal.
5. 12. 50 Urine—1,100 ml./24 hrs; arsenic content—0.14 mg./24 hrs specimen of urine.
12. 12. 50 Hair—Arsenic content—115 µg./100 g.
12. 12. 50 Urine—No arsenic present.
15. 12. 50 Blood urea—21 mg./100 ml.
Plasma fibrinogen—0.34 g./100 ml.
17. 12. 50 Wassermann reaction—negative.
Price's precipitation reaction—negative.
Cholecystogram—Normal functioning gall bladder. No radio-opaque stones seen.
18. 12. 50 *Leptospira icterohaemorrhagiae*—Tests negative.

Liver biopsy was not performed.

Treatment.—A high protein, high carbohydrate, and low fat diet, with vitamin B supplements, was administered. On 6. 12. 50, as soon as it seemed probable that the jaundice was due to arsenic, treatment with BAL was commenced, 2 ml. being given four-hourly on the first day, twice daily on the second and third days, and once daily on the fourth to seventh days.

There were no toxic effects, and after the first day, the patient volunteered that "she had had the best night's

* Received for publication May 3, 1951.

TABLE
LIVER FUNCTION TESTS

Date	1.12.50	10.12.50	28.12.50	22.1.51
Van den Berg qualitative	Direct positive	Direct positive	Direct positive	Negative
Alkaline phosphatase (units)	30	25	23	7
Bilirubin mg./100 ml.	30.4	8.0	2.3	1
Albumin g./100 ml.	3.5	3.6	4.0	4.0
Globulin g./100 ml.	3.9	4.2	3.0	2.8
Gamma globulin g./100 ml.	2	1.1	1.0	0.8
Thymol turbidity (units)	2	4	3	2
Cephalin cholesterol	Negative	Negative	Negative	Negative
Colloidal gold	Negative	Negative	Negative	Negative
Ester mg./100 ml.	450	1,580	820	92
Free mg./100 ml.	330	260	260	38

rest since becoming jaundiced". Three days later the pruritis disappeared. Recovery was uneventful and she was discharged from hospital on 22. 1. 51.

Differential Diagnosis

The following possibilities were included :

- (1) Infective hepatitis.
- (2) Extrahepatic obstructive jaundice.
- (3) Homologous serum jaundice.
- (4) Arsenical jaundice.

Homologous serum jaundice could be ruled out from the absence of any history of intravenous or other serum therapy.

Infective Hepatitis.—The clinical history and examination were against this diagnosis. Usually the onset is more insidious, and anorexia is present for some time before the onset of clinical jaundice. The absence of enlargement or tenderness of the liver at any time during the illness almost excludes the diagnosis. Angioneurotic oedema does not usually precede infectious hepatitis. The degree of jaundice was out of keeping with the relative well-being of the patient. The pruritis was extreme whereas in infective hepatitis this is absent or slight. Empirical liver function tests (see Table) were consistently negative.

Extrahepatic Obstructive Jaundice (Surgical Jaundice).—The clinical picture and the liver function tests were in favour of an obstructive jaundice ; (e.g., amount of serum bilirubin present, high cholesterol figure, negative empirical liver function

tests, deep yellow-green jaundice, pruritis, absence of urobilinogen from urine). Against the diagnosis were the absence of any previous history of cholecystitis, cholelithiasis, or pain, and the normal cholecystogram.

Arsenical Jaundice.—Two groups of jaundice during arsenical therapy are described, but they have been somewhat confused in the past. This is understandable, in that it is only during the past few years that a virus or group of viruses has been proved to be the causative agents of infectious hepatitis and homologous serum jaundice. The latter is usually transmitted by the intravenous injection of blood or blood products or by the use of syringes contaminated with blood containing the virus during intravenous administration of arsenic. The present case does not fall into this category but seems to belong to the obstructive jaundice group, being probably due to the intrahepatic obstruction of the bile ducts.

Discussion

The case described produced a clinical picture and liver function tests similar, if not identical, to a small group of cases described by Hanger and Gutman (1940). These cases followed the intravenous injection of arsphenamine whereas this case followed the vaginal application of acetarsol. That arsenic was probably the cause of the jaundice, was proven by the finding of arsenic in the hair and urine, and also by the remarkable relief of pruritis and disappearance of jaundice by the administration of BAL.

This group forms a clear-cut clinical, biochemical, and pathological picture, which distinguishes it from other forms of parenchymatous jaundice, but from which the diagnosis of an extrahepatic obstructive "surgical" jaundice can be an extremely difficult problem.

Steigmann and Popper (1943) described a series of cases of intrahepatic obstructive jaundice which included cases of catarrhal jaundice, arsenical jaundice, infectious hepatitis, toxic jaundice, cinchophen jaundice, and cirrhosis of the liver. It is not clear whether there were not in fact some cases of syringe jaundice (homologous serum jaundice) in the arsenical group, and it is therefore difficult to differentiate the two groups of arsphenamine jaundice in this series. However, there is the significant statement that the relative incidence of the obstructive phenomenon appears highest in the cases of arsphenamine hepatitis, in which group 36 per cent. of cases were of the obstructive type.

It is well known that obstructive phenomena appear in some cases of infectious hepatitis, but the history, liver function tests, and biopsy findings differ from the cases described by Hanger and Gutman (1940) in which there was no significant parenchymatous damage.

Clinical Characteristics of Post-arsphenamic Jaundice apparently due to Obstruction of the Intrahepatic Biliary Tract.—Hanger and Gutman (1940) describe in detail the symptomatology of these cases which all follow a similar pattern. This type of reaction usually occurs in patients receiving intravenous arsphenamine therapy for the treatment of syphilis. The first intravenous injection is without incident, but reactions follow the second or third injection, after an interval of 2 to 10 hours. The jaundice in the case presented occurred after seven days on acetarsol pessaries. That syphilis is not the cause of the reaction is shown by its absence in one of the cases described by Hanger and Gutman (1940), and also in the present case.

There is an acute onset of symptoms, consisting of rigors, fever, malaise, headache, and vertigo. This is followed by nausea, vomiting, and anorexia. There may be a conjunctivitis with chemosis, and a transitory morbilliform or scarlatiniform eruption at the onset of the illness. Diffuse muscle pains and fleeting arthralgias may occur. Diarrhoea, colicky abdominal pains, and oedema of the face or extremities may also develop.

Jaundice does not appear for some days after the beginning of the illness and is of the obstructive type, with dark urine and pale stools, and absence of urobilinogen. Pruritis develops at about this time; it is severe and constantly present so long as the

jaundice continues, and is, indeed, the predominant symptom of the whole illness. Loss of weight may occur, and the patient may be listless if the jaundice persists for any length of time. Hepatosplenomegaly may occur. In the initial stages of the disease there is a leucocytosis with an eosinophilia. Complete recovery is the rule.

Biochemical Characteristics of Post-arsphenamine Jaundice of the Obstructive Type.—Empirical liver function tests are usually normal, and the serum alkaline phosphatase usually exceeds 10 units. The total cholesterol content of the blood serum tends to rise in patients with the obstructive phenomenon, and may reach extraordinarily high levels, whereas normal or low values are observed in patients with homologous serum jaundice. In many cases the upward trend in serum cholesterol levels becomes more marked in the recovery phase, when serum bilirubin values begin to fall. The reason for this is not known. A slight rise in serum globulin is sometimes noted later in the disease. Non-protein nitrogen and blood urea are usually normal.

The pathology, as determined by a few cases of liver aspiration and laparotomy, shows:

- (1) absence of significant parenchymal degeneration in intensely jaundiced patients,
- (2) cholangitis and pericholangitis of the non-suppurative type,
- (3) presence of bile plugs in many of the bile capillaries, suggesting that the finer biliary radicles are the chief site of injury. Inflammatory changes around the bile passages and bile thrombi within the lumen of the canaliculi were apparently the cause of the obstructive jaundice (Hanger and Gutman, 1940).

Steigmann and Popper (1943) believe the mechanism of the obstructive phenomenon to be a toxic exudative reaction affecting the periportal field with compression of the junction between the bile capillaries and bile ducts, or of the canal of Hering.

Selective injury of the finer biliary radicles, which is so striking in the liver biopsies of the arsphenamine cases described, may be produced by a number of toxic agents. It has been noted in experimental toluylene diamine poisoning, a condition found by Bodansky (1937) to be associated with unusually high serum phosphatase and cholesterol values. Dinitrophenol may also cause jaundice similar to that due to arsphenamine.

There has been much speculation as to the cause of the arsenical reaction, e.g. the Jarisch-Herxheimer phenomenon, hepatic syphilis, erythema of the ninth day, and overdosage of arsphenamine. In the present case, there was no clinical evidence of syphilis and the Wassermann reaction was negative. The general pattern of the reaction has certain characteristics of drug hypersensitivity; for example,

the initial injection of arsphenamine is without incident unless arsphenamine has been administered previously, but symptoms are precipitated by the second and third injections after a short latent period. In this case symptoms occurred after pessaries had been administered for four days.

Systemic reaction due to the absorption of arsenic following acetarsol pessaries has been recorded. Campbell (1937) and Long (1937) have described cases of skin eruptions due to absorption of small amounts of arsenic in hypersensitive subjects.

Summary

- (1) A case of obstructive jaundice, following the

use of acetarsol pessaries, and probably due to intrahepatic obstruction of the bile ducts, is presented.

- (2) The clinical, biochemical, and pathological characteristics of this type of jaundice are described.

- (3) The causation of this reaction is discussed.

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ANNOUNCEMENT

A special meeting of the Filiale Marseillaise de la Société Française de Dermatologie et de Syphiligraphie will be held in the University Dermatological Clinic at the Hôtel-Dieu, Marseille, on October 19, 20, and 21, 1951. Papers on "The organic non-specific reactions and their incidence in dermatology" will be presented.

Further details can be obtained from Dr. J. Bonnet, the General Secretary of the Society at the above address.